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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/333,248 06/15/99 VAN DER KOOY

D 08589/002002

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HM12/0411

EXAMINER
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YUCEL, I

ART UNIT	PAPER NUMBER
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1636

DATE MAILED:

04/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

**Office Action Summary**

Application No.

09/333,248

Applicant(s)

VAN DER KOOY ET AL.

Examiner

Yucel Remy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 January 2001.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 5-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 5-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☒ Other: *detailed action*.

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### **DETAILED ACTION**

Claims 5-8 are pending in the application. This Office action is in response to the amendment filed 12 January 2001.

#### ***Response to Amendment***

Claims 5-8 stand rejected under 35 U.S.C. § 112, first paragraph (enablement) for the reasons made of record in the Office action mailed 17 July 2000.

The rejections of claims 2-4 35 U.S.C. § 112, second paragraph have been rendered moot in light of cancellation of these claims.

The objection to claim 1 has been withdrawn in light of cancellation of this claim.

#### ***Response to Arguments***

It is first noted that Applicants start their arguments with a seemingly unsubstantiated statement regarding a preferred technique for transplanting retinal cells into the vitreous of the eye. It is also noted that there also does not appear to be support in Applicant's specification for this proposition. Second, there is no evidence provided by Applicant that is the preferred site/technique for retinal stem cells. Finally, the relevance of the statement to the present rejection is not clear to the Examiner.

Applicant's first argument is that "the majority of transplant studies using models clearly demonstrate the feasibility and success of transplanting embryonic and non-embryonic RPE cells. Mitigating undesired immune reactions is not a significant barrier when dealing with transplanted RPE tissue in or near the retina." Applicant summarizes the references cited by the Examiner to reach this conclusion. This argument has been considered but is not found persuasive for the reasons already made of record and the following discussion. Applicant

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appears to be arguing that the Grisanti reference illustrates the utility of transplantation; this was never an issue in the present rejection which is for enablement. Applicant's claims go beyond mere transplantation (to see (no pun intended) what will happen to RPE cells once they are placed into an animal) to treatment of various different and unrelated conditions. Thus, the teachings in Applicant's specification must also teach the skilled artisan how to overcome the hurdles (previously documented in the prior art) to achieve the claimed invention.

Contrary to Applicant's assertions, the reoccurring theme of the Grisanti reference is that RPE cells do induce immune responses. The Grisanti reference was published about the same time as Applicant's effective filing date. In the first sentence of the discussion, they teach that therapeutic transplantation is likely to become (i.e. in the future) one of the major achievements in ophthalmology. At page 1625, first column, they offer two explanations why they did not observe uveitis. One is that their examination time was too short or simply without adjuvants, there is no sufficient response. They also discuss the role of ACAID, but they also teach that it is not known if ACAID would be overcome with persistent exposure to immunogenic factors (such as would be the case of transplanted cells which survive in the long term). They also raise concerns about the long term effects of ACAID, if it is not overcome: specifically they caution that significant side effects such as fibrosis triggered by transforming growth factors may result. The jury is still out with respect to the possibilities raised by Grisanti and they admit that their results are not conclusive of an absence of an immune response, nor can they predict that a persistent, protective ACAID will not eventually be overcome or if the long term effects of ACAID will not result in equally difficult side effects. All in all, the teachings of Grisanti illustrate the highly unpredictable nature of the art of (stem) cell transplantation of the eye and

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that there are many unanswered questions which need to be resolved before successful protocols can be developed.

In their abstract, Enzmann et al. teach that immune responses in the posterior part of the eye do occur, contrary to Applicant's unsupported assertions made in the opening remarks. Applicant then cites a passage on page 180 which allegedly illustrates how immune responses may be reduced by separation of activated RPE cells. However Applicant fails to indicate where in the present specification there is support for these teachings. Applicant is reminded that the claimed invention must be enabled as of its effective filing date. Secondly, it is not clear if one may predictably extrapolate these teachings to retinal stem cells since Applicant's claims are not limited to RPE cells. Enzmann et al. also extend the teachings of Grisanti vis a vis ACAID, see page 181, where they teach that ACAID is not absolute and thus, there is no true immunologically privileged site in the eye. They also teach (see middle of first column, page 181) that "In vivo, the situation of MHC class I and II expression is probably different since the cells in the transplantation area are additionally stimulated via the surgical trauma and its inflammation and/or secretion of growth factors, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) by glial cells." Enzmann conclude by stating "Many immunological questions must be answered, however, before extensive efforts in patients are possible and before rejection is no longer a major barrier to successful retinal transplantation." Clearly, this indicates that the art at the time of the invention and even after, recognized immunological responses as a major hurdle to success.

The point that Applicant makes with regard to the Craaford (not Crawford) reference has been considered but is not found persuasive because of the teachings found in the second column

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on page 252 which illustrate that macrophages act as APC cells under certain circumstances.

Thus, while this may not be an immunological response *per se*, it is the function<sup>a</sup> equivalent.

Whether one interprets this as an immunological response or a macrophage response, the end result still remains that the cells are rejected and that there is no long term survival of the transplanted cells and that photoreceptor degeneration occurs in areas adjacent to the sites of rejection.

Finally, Applicant is referred to page 1005 of Valtink where cell transplantation is discussed. Valtink teach that immunological failure must be prevented for successful methods to be developed and that there is a possibility of graft failure (as suggested by Craaford). Thus, the Examiner's assertions are supported by the reference.

Applicant concludes the argument that those skilled in the art are able to transplant retinal stem cells just as efficiently as the more routine RPE transplants. It appears then that the conclusion to be drawn is that no further guidance in the specification is needed and that the claimed invention is enabled. This final argument has also been considered, but not found persuasive for the following reasons. First, it is not clear to which art Applicant is relying upon for the teachings that stem cell transplantations are performed routine,<sup>h</sup> especially given the teachings on page 8 of the specification, line 23, where Applicant states "the prior art teaches that it is highly unlikely that there is a retinal stem cell." Applicant cannot "have it both ways". Either the stems do not exist--and therefore, transplantation of said cells do not exist, let alone "be routine." Or that they do exist prior to Applicant's effective filing date. Applicant has not provided support for this contention. Second, in light of the discussion of the cited papers both in the Office action mailed 17 July 2000 and above, the skilled artisan would not accept on its

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face the proposition that retinal stem cells or cells differentiated from these cells could be transplanted without avoiding the significant hurdles explicitly taught by the cited references such that the vastly different conditions recited in the present claims would be treated or ameliorated. In absence of detailed teachings from the specification, the skilled artisan would resort to trial and error experimentation to practice the claimed invention and this level of experimentation in this demonstrably unpredictable field would be undue. The claims, therefore, stand rejected.

### *Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph.D. whose telephone number is (703) 305-1998. The examiner can normally be reached on Monday-Friday, 8:00am-4:30 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0044. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Patent Analyst Dianiece Jacobs whose telephone number is (703) 305-3388.



Remy Yucel, Ph.D.  
Primary Examiner  
Art Unit 1636

ry  
April 9, 2001